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**Statin Treatment, Phenotypic Frailty and Mortality Among Community-Dwelling Octogenarian Men:
The Helsinki Businessmen Study (HBS) cohort**

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Keywords:	cholesterol, cardiovascular disease, metabolic, nutrition, prealbumin
Keypoints:	Community-living octogenarian statin users have survival benefit despite multimorbidity and may be associated with nutrition, Possible contributor to the resilience with statins was the significantly higher prealbumin level pertaining to better nutrition, Phenotypic frailty and quality of life measurements showed non-significant differences among statin users and nonusers

Statin Treatment, Phenotypic Frailty and Mortality Among Community-Dwelling Octogenarian Men:

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Abstract

Background: Statin treatment has increased also among people aged 80 years and over, but adverse effects potentially promoting frailty and loss of resilience are frequent concerns.

Methods: In the Helsinki Businessmen Study (HBS), men born in 1919-1934 (original n=3490), have been followed-up since the 1960s. In 2011, a random subcohort of home-living survivors (n=525) was assessed using questionnaires, and clinical (including identification of phenotypic frailty) and laboratory examinations. A 7-year mortality follow-up ensued.

Results: We compared 259 current statin users (median age 82 years, interquartile range 80 to 85 years) with 266 nonusers (83; 80 to 86 years). Statin users had significantly more multimorbidity than nonusers (prevalencies 72.1% and 50.4%, respectively, $P<0.0001$) and worse glucose status than nonusers (prevalencies of diabetes 19.0% and 9.4%, respectively, $P=0.0008$). However, there was no difference in phenotypic frailty (10.7% vs 11.2%, $P=0.27$), and statin users had higher plasma prealbumin level than nonusers (mean levels 257.9 and 246.3 mg/L, respectively, $P=0.034$ adjusted for age, body mass index and C-reactive protein) implying better nutritional status. Despite morbidity difference, age-adjusted 7-year mortality was not different between the two groups (98 and 103 men among users and nonusers of statins, respectively, hazard ratio 0.96, 95% confidence interval 0.72-1.30).

Conclusions: Our study suggests that male octogenarian statin users preserved resilience and survival despite multimorbidity, and this may be associated with better nutritional status among statin users.

Key words: cholesterol, cardiovascular disease, metabolic, nutrition, prealbumin, older people.

Keypoints:

Community-living octogenarian statin users have survival benefit despite multimorbidity and may be associated with nutrition.

Possible contributor to the resilience with statins was the significantly higher prealbumin level pertaining to better nutrition.

Phenotypic frailty and quality of life measurements showed non-significant differences among statin users and nonusers.

Although randomised treatment trials are lacking, statin treatment is common among octogenarians (1, 2). In any age group, effects of treatments on overall health status, functioning and wellbeing are important to consider (1). Several concerns on statin treatment in older people, especially over 80 years of age, have been expressed, and these include risk of musculoskeletal pain impairing function, development of diabetes (2, 3, 4, 5, 6), and the epidemiologic finding of low cholesterol associating with higher mortality (7, 8). It is thus feared that statin treatment -- despite beneficial effects in younger adults -- could impair resilience among oldest-old patients.

However, cholesterol levels may decrease in older people because of nutritional deficiencies or unintentional weight loss (one component of frailty), and chronic diseases leading to inflammaging (9, 10). We have previously reported from the Helsinki Businessmen Study (HBS, a cohort of men born in 1919-1934) that statin treatment is not associated with impaired health-related quality of life (HRQoL) in octogenarian men (11). Moreover, there was less weight loss in older statin users compared to nonusers (12), which may be a favourable feature in people prone to frailty. Interestingly, hydroxymethyl coenzyme A reductase (HMGCR) gene variation has been reported to be associated with higher body-mass index (BMI), which could also affect type 2 diabetes risk (T2DM) (13). Statin treatment and HMGCR gene variation were both associated with body weight gain and higher risk for T2DM, but the magnitude of body-weight change was insufficient to account for the increased T2DM risk. Furthermore, the link between the reported gene variation and insulin/glucose concentrations supported body-weight mediated association of HMGCR inhibition with insulin resistance.

In the present analysis we aimed to characterise multidomain associations of statin treatment with lifestyle, frailty and morbidity, as well as nutritional, metabolic, and inflammatory markers, among community-dwelling octogenarian men of the HBS cohort. We also related statin use to 7-year mortality follow-up.

Methods

Study Population and Measurements

These are secondary analyses of the HBS, a cohort of men born 1919 to 1934 (original n=3490), who have been followed-up since the 1960s. Their cardiovascular disease risk factor history (including fasting serum cholesterol and one-hour post-load glucose values) is known since midlife (mean age 40 years), and the cohort has been followed-up with regular postal questionnaires including reported medication since the year 2000 (14). In 2010/11, current addresses were retrieved from the Population Information System of Finland for 907 surviving HBS participants, and a questionnaire survey about lifestyle, medications, prevalent physician-diagnosed diseases, and HRQoL (RAND-36/SF-36 instrument, https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html, 11) was sent to them.

In that wave, the questionnaire was returned by 615 men (67.8% response rate), and clinical and laboratory examinations were performed in a random subcohort of 525 men (consort diagram is shown in Appendix Figure 1). Statin users and nonusers were compared using multidomain variables presented in Appendix Table 1. Body mass index (BMI) was defined as weight (kg) divided by midlife height (m) squared), waist circumference was measured at the upper level of the pelvic crest. Morbidity was assessed from nine self-reported diseases (diabetes, hypertension, coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, chronic obstructive lung disease, cancer, and musculoskeletal disease) and multimorbidity was defined as 2 or more concomitant diseases. The prevalence of phenotypic prefrailty and frailty was assessed using a modified Fried method as described earlier (15). A total score of 3 or more defined frailty, a score of 1 or 2 defined pre-frailty, and 0 indicated nonfrailty. Peak expiratory flow (PEF) was measured 3 times and mean value used for analyses.

Walk speed was measured in 10 meters. Laboratory examinations were performed after a 12 h fast and analysed by the certified laboratory of the Oulu University Hospital (Oulu, Finland). Indices were calculated to reflect glucose metabolism: quantitative insulin sensitivity check index ($QUICK = 1 / \log(\text{fasting insulin } \mu\text{U/mL}) + \log(\text{fasting glucose mg/dL})$), and homeostatic model assessment – insulin resistance (HOMA-IR with glucose in molar units = $[\text{glucose} \times \text{insulin}]/22.5$).

Total mortality up to 31 March 2018 was retrieved from the Finnish Population Information System. The follow-up has been approved by the ethical committee of the Department of Medicine, Helsinki University Hospital. The study is registered as ClinicalTrials.gov identifier: NCT02526082.

Statistical Analysis

Descriptive statistics, Armitage test for trend in proportions, and analysis of covariance (ANCOVA) were used to compare statin users with nonusers. The ANCOVA analyses (reporting means with standard errors [SE] in the statistical package) were primarily adjusted for age to study multidomain variables. The analysis

of prealbumin among statin users and nonusers was further adjusted for age, BMI and C-reactive protein (CRP). RAND-36 scales were analysed using ANCOVA to compare statin users and nonusers and were primary adjusted for age, multimorbidity was added in the model when feasible. Multiple testing was adjusted using Bonferroni's correction procedure. Assumptions of Cox regression were met and it was used to study proportional hazard ratios [HR] with 95% confidence intervals [CI] for factors affecting follow-up mortality. The model included statin usage, age and was additionally adjusted for midlife cholesterol and current morbidity. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using NCSS statistical software (Kaysville, UT, www.ncss.com, version 8).

Results

We compared the 259 men currently on statin treatment (median age 82, interquartile range 80 to 85 years) with the 266 men not using statins (median age 83; interquartile range 80 to 86 years); their multidomain characteristics are compared in Table 1. Of the statin users in 2010/11, 32.3% and 91.8% reported statin use also in 2000 and 2007, respectively; among nonusers the respective proportions were 3.8% and 19.2%. Overall, statin users were sicker than nonusers, especially for cardiovascular diseases and diabetes. Consequently, statin users had also more multimorbidity than nonusers (prevalence 72.1% versus 50.4%, $P < 0.0001$).

As expected, statin users had clearly lower total cholesterol and LDL cholesterol levels (mean [SE]: 2.3 [0.05] versus 3.1 [0.05] mmol/L, $P < 0.0001$), but lower HDL cholesterol (1.49 [0.03] versus 1.57 [0.03] mmol/L, $P = 0.026$), respectively. On the other hand, indices related to glucose metabolism tended to be worse among statin users, who also had a twice higher prevalence of diabetes as compared to nonusers (19.0% vs. 9.4%, $P = 0.008$), despite similar BMI and waist circumference. One-hour post-load glucose level measured in midlife was similar in users and nonusers of statins (mean 6.0, SE 0.1 mmol/L in both groups). Interestingly, plasma prealbumin level reflecting nutritional status was significantly ($P = 0.005$) higher among statin users (257.9 [2.9] mg/L) than nonusers (246.3 [2.9] mg/L). The difference remained significant ($P = 0.034$) when adjusted further for BMI and plasma high-sensitivity C-reactive protein level.

Decreasing prealbumin showed a trend ($P = 0.050$) for age-adjusted association with frailty in the whole cohort. Furthermore, highly significant ($P < 0.0001$) age-adjusted decrease of peak expiratory flow (PEF) was seen with increasing frailty.

However, no significant differences between statin users and nonusers were observed for various frailty indicators, including phenotypic frailty. Of note, statin users also reported significantly less musculoskeletal disorders than nonusers ($P = 0.048$). We also compared the 8 scales of RAND-36 HRQoL instrument between statin users and nonusers, and after adjustment for age and multimorbidity, there was no significant difference in any of the HRQoL scales (Table 2).

During the 7-year follow-up (2011-2018), 198 men (37.7%) died, 95 (36.7%) and 103 (38.7%) among statin users and nonusers. Age-adjusted HR of statin use was 0.96 (95% CI 0.72 to 1.30, $P = 0.81$). Further

adjustment for current morbidity and midlife cholesterol (to reflect life-course cholesterol burden: mean 6.7, SE 0.07 mmol/L and 6.1, 0.07 mmol/L among users and nonusers of statins in 2010/11, respectively, $P < 0.0001$) diminished the point estimate but failed to reach statistical significance (HR 0.80, 95% CI 0.58 to 1.11, $P = 0.19$). Of note, multimorbidity in the whole cohort in 2010/11 was associated with a significant 41% increase of 7-year total mortality (HR 1.41, 95% CI 1.03 to 1.94, $P = 0.03$).

Discussion

In a real-life setting of a socioeconomically homogenous group of community-living octogenarian men, statin users had significantly more multimorbidity and derangement of glucose metabolism than nonusers. Still, statin users were not more frail, their quality of life was not impaired, and they had a similar mortality rate during a 7-year follow-up as compared to generally healthier nonusers of statins. A possible contributor to the resilience of statin users was the significantly higher prealbumin level pertaining to better nutritional health, a very important health factor among people aged 80 years and older.

The present results further strengthen the evidence that statins are effective and safe way to improve prognosis also in octogenarians who have increased atherosclerotic cardiovascular disease (ASCVD) burden and risk factors and may thus relieve important concerns of statin use among oldest patients. Despite midlife cholesterol and current morbidity, the follow-up for 7-years showed a slight non-significant trend for statins decreasing overall mortality among men who were overrepresented with ASCVD. Our results are in accordance with a recent large meta-analysis of statins at different ages and among older individuals (16). Although statins were shown safe and effective in all age groups, the direct evidence for primary prevention among older people is less clear whilst statin therapy should be used by those with high risk for ASCVD. Our results support earlier studies showing neutral or improved effects of statin treatment irrespective of factors related to frailty, pains, HRQoL, or cognitive function in old age (3, 5, 17 - 22).

A new and interesting finding among home-living statin users was the significantly higher plasma prealbumin level, which was independent of both BMI and C-reactive protein. Prealbumin has been used as an indicator of nutritional status (23), but it is also a negative acute-phase protein (24). Lower prealbumin levels have been reported to be associated with increased sarcopenia prevalence in older hospitalised patients independently of BMI and age (25, 26). Prealbumin levels below inflection point 265.9 mg/L were negatively associated with sarcopenia in hospitalised Chinese patients (26). Of note, in our study the mean prealbumin levels among statin users and nonusers were consistently fitted in the range and thereby independent association of nutritional marker with frailty vulnerability can be assumed. Prospective studies with severe specific morbidities have reported survival benefit with increasing level of prealbumin (27, 28), and among patients with heart failure, less statin use was associated with lower plasma prealbumin levels (28). We suggest that resilience and survival of older statin users would be at least partly associated with better preserved nutritional status reflected by higher prealbumin. There is also question arising whether statin-induced diabetes might reflect better nutrition and consequent resistance to the development of frailty. Detailed mechanisms underlying the finding need to be clarified in further studies.

There are several limitations in our study. The homogeneity of the cohort is a strength (as it constricts variation in potential confounding factors) but also a limitation, in particularly in terms of the generalisability of findings. As the results apply to men and the response rate was 67.8% it is likely that non-responders may produce bias where the most frail people are underrepresented. Although with frequent multimorbidity, one third of the cohort was assessed to be nonfrail. Also, the HRQoL in the cohort was relatively good. The results may thus not apply to most frail and institutionalised patients, although some epidemiologic studies have reported that prognostic benefit of statin treatment is independent of frailty status (17, 18). The survivorship bias needs to be accounted for as individuals with increased risk have been prescribed for statins causing unexpectedly lower mortality and more cardiovascular co-morbidities. Moreover, the relationship of prealbumin with nutritional status may be confounded by clinician assessed indication and patient adherence. The exact duration of statin treatment was not known, but our earlier questionnaire surveys suggest that majority had been on a statin for at least 3 years, and a third for 10 years (unpublished observations). Among nonusers, 20% have been using statins earlier, but reasons for discontinuation are not known.

Conclusions

Among octogenarian men, statin use is associated with factors related to preserved resilience and survival despite more multimorbidity. The results may warn against deprescribing statins based on age alone.

Declarations of Sources of Funding:

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Declarations of Conflicts of Interest

Dr TE Strandberg reports various cooperation (educational, research, consultation) with several companies marketing cholesterol-lowering drugs including Amgen, AstraZeneca, Merck, OrionPharma, Pfizer, Servier. Minor stock in OrionPharma (listed company). Other authors declare no conflict of interest related to this paper.

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Table 1. Characteristics of participants by statin use^a.

variable	Nonusers, n=266	Statin users, n=259	P-value
age, y, median (interquartile range)	83 (80-86)	82 (80-85)	0.073
Lifestyle			
ever smokers, n (%)	125/265 (47.2)	108/257 (42.0)	0.12 (trend)
nondrinker, n (%)	52 (19.8)	54 (21.0)	0.36 (trend)
economic status good to satisfactory, %	99.7	100	0.77
daily walking distance, %			0.81 (trend)
- 0	1.2	3.0	
-< 1 km	29.1	26.1	
-1-3 km	55.0	56.0	
>3 km	14.7	17.1	
Nutrition			
BMI, kg/m ²	24.8 (0.2)	25.1 (0.2)	0.18
waist circumference, cm	96.4 (0.6)	97.3 (0.6)	0.29
prealbumin, mg/L	246.3 (2.9)	257.9 (2.9)	0.005 ^b
lipids, mmol/L			
- total cholesterol	5.2 (0.06)	4.4 (0.06)	<0.0001

- triglycerides	1.23 (0.04)	1.31 (0.04)	0.13
- HDL cholesterol	1.57 (0.03)	1.49 (0.03)	0.026
- LDL cholesterol	3.1 (0.05)	2.3 (0.05)	<0.0001
Metabolic			
glucose, mmol/L	5.7 (0.09)	6.0 (0.09)	0.056
insulin, mU/L	13.0 (0.9)	15.5 (0.9)	0.054
HOMA-IR, (glucose mmol/L x insulin mIU/L)/22.5	3.53 (0.33)	4.36 (0.33)	0.077
QUICK1, 1 / log(fasting insulin µU/mL) + log(fasting glucose mg/dL)	0.34 (0.003)	0.33 (0.003)	0.029
urate, µmol/L	376.1 (5.6)	390.2 (5.6)	0.077
Inflammation			
hs-CRP, mg/L	2.8 (0.4)	2.6 (0.4)	0.21
Frailty			
PEF L/min	441.2 (5.9)	439.6 (5.9)	0.85
ALT U/L	18.7 (0.5)	18.8 (0.5)	0.93
creatinine, µmol/L	95.8 (1.9)	99.3 (1.9)	0.19
walk speed, m/s	0.86 (0.01)	0.84 (0.01)	0.39
phenotypic frailty assessed			0.27 (trend)

in 511 men, n (%)			
-nonfrail	92 (35.7)	97 (38.3)	
-prefrail	137 (53.1)	129 (51.0)	
-frail	29 (11.2)	27 (10.7)	
Morbidity, n (%)			
-diabetes	25 (9.4)	49 (19.0)	0.0008
-hypertension	120 (45.1)	155 (59.8)	0.0007
-CAD	19 (7.1)	117 (45.3)	<0.0001
-cerebrovascular disorder	25 (9.4)	55 (21.2)	<0.0001
-PAD	27 (10.2)	30 (11.6)	0.29
-heart failure	35 (13.2)	52 (20.2)	0.02
-chronic lung disease	28 (10.5)	29 (11.2)	0.40
-cancer	62 (23.3)	46 (17.8)	0.06
-musculoskeletal disease	118 (44.4)	96 (37.2)	0.048
mean number of diseases	1.7 (0.08)	2.4 (0.08)	<0.0001
multimorbidity (≥ 2 diseases)	134 (50.4)	186 (72.1)	<0.0001

Notes: Continuous variables are mean (SE). ALT = alanine amino transferase; BMI = body mass index; CAD = coronary artery disease; hs-CRP = high sensitivity C-reactive protein; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; PAD = Peripheral artery disease; PEF = peak expiratory flow; QUICK 1 = Quantitative Insulin Sensitivity Check Index.

^aAdjusted for age; analysis of covariance (ANCOVA) for continuous variables, Armitage test for trend in proportions. Logarithmically transformed values of triglycerides and C-reactive protein were used for comparisons.

^bP=0.034 after further adjustment for BMI and hs-CRP

Table 2. Age-adjusted RAND-36 scales by statin use.

Scale ^a	Nonusers, n=266	Statin users, n=259	P-value ^b
Physical Function	74.9 (1.3)	74.2 (1.4)	0.71
Role Physical	71.4 (2.3)	68.4 (2.3)	0.35
Role Mental	80.3 (2.0)	78.3 (2.1)	0.48
Perceived Pain	80.6 (1.2)	80.5 (1.2)	0.94
Vitality	76.5 (0.9)	75.7 (0.9)	0.57
Social Function	87.1 (1.2)	85.0 (1.2)	0.21
Mental Health	84.3 (0.9)	83.4 (0.9)	0.43
General Health	61.7 (1.1)	57.9 (1.1)	0.015 ^c

^a Scores are mean (SE), range from 0 (worst) to 100 (best).

^b Analysis of covariance (ANCOVA)

^c P=0.43 after further adjustment for multimorbidity

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Appendix Figure 1. Consort diagram of the study.



n = 103

n = 95

Appendix Table 1. Multidomain variables assessed in 525 HBS participants in 2010/11.

Lifestyle-related
Smoking
Alcohol use
Economic status
Physical activity
Nutrition- or Metabolism-related
BMI
Waist circumference
Laboratory variables (plasma lipids, prealbumin)
Glucose metabolism (plasma glucose, insulin, HOMA and QUICK indexes)
Urate
Inflammation-related
High-sensitivity C-reactive protein
Frailty-related
Peak-expiratory flow (PEF)
Walk speed
Laboratory variables (plasma ALT, creatinine)
Phenotypic frailty
Morbidity
Self-reported diseases
Multimorbidity

